Lonsurf (Trifluridine plus Tipiracil): A New Oral Treatment Approved for Patients with Metastatic Colorectal Cancer

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Considering its high financial and personal costs, colorectal cancer continues to be a major public health problem in the United States and around the world.[1] Colorectal cancer is the second leading cause of cancer death in the United States when data are combined for men and women.[1] The American Cancer Society estimates that approximately 134,490 Americans will be diagnosed with colorectal cancer in 2016, and an estimated 49,190 people will die from this disease.[1]

Improvements in the screening and treatment of colorectal cancer have favorably affected patient outcomes, such that the death rates have declined significantly in the past 20 years.[1] Colorectal cancer is curable if diagnosed early.[2] The 5-year survival rates for patients with stage I disease exceed 90%.[2]

Surgery, radiation therapy, chemotherapy, and targeted therapies are viable alternative treatment options for patients with colorectal cancer. These modalities can be used in sequence or in combination to optimize the responses and long-term outcomes, depending on the disease stage.[3] Systemic therapy options for patients with metastatic colorectal cancer that is not amenable to surgical resection or radiation include cytotoxic chemotherapy and targeted therapies.[3] Frequently used chemotherapy regimens for metastatic colorectal cancer include FOLFOXIRI (leucovorin, 5-fluorouracil [5-FU], oxaliplatin, and irinotecan); FOLFOX (leucovorin, 5-FU, and oxaliplatin); FOLFIRI (leucovorin, 5-FU, and irinotecan); CapeOx (capecitabine and oxaliplatin); and FL (5-FU and leucovorin); as well as single-agent capecitabine, and irinotecan.[3]

The National Comprehensive Cancer Network Clinical Guidelines for colorectal cancer recommend the adjunctive use of targeted agents with specific first-line and subsequent therapies, noting that this strategy improves the efficacy outcomes, although it increases the toxicity rates among patients with colorectal cancer.[4] Currently available targeted therapies for colorectal cancer are mostly administered intravenously (**Table 1**).

Colorectal cancer is one of the most costly tumor types to manage, second only to breast cancer in the United States.[5] Of the more than $124 billion spent on cancer care in 2010 in the United States, colorectal cancer represented $14 billion, or approximately 11%.[5] By the year 2020, the costs associated with colorectal cancer in patients aged ≥65 years are projected to increase by at least 53%, such that the economic burden of this cancer will be substantial, particularly among Medicare beneficiaries.[6]

Although advances in the screening, prevention, and genomic analysis, as well as the management of colorectal cancer have had an important impact on patient outcomes, including overall survival, a high proportion of patients with advanced stages will die from this disease.[2] The statistics are particularly dire for patients with metastatic cancer; the 5-year survival rate is only 11% in this patient subgroup.[2] Additional treatment advances are needed for patients with metastatic colorectal cancer.

A New Oral Option for Metastatic Colorectal Cancer

On September 22, 2015, the US Food and Drug Administration (FDA) approved a novel oral agent that combines 2 drugs, trifluridine and tipiracil (Lonsurf; Taiho Oncology), for the treatment of patients with metastatic colorectal cancer who have received fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF (vascular endothelial growth factor) biologic therapy, and, if *RAS* wild-type, an anti-EGFR (epidermal growth factor receptor) therapy.[7,8]

Trifluridine plus tipiracil (previously TAS-102) is the second oral agent approved by the FDA for metastatic colorectal cancer.[7] The first oral agent in this setting, regorafenib (Stivarga), was approved in September 2012.[9]

The approval of trifluridine plus tipiracil was based on results of the RECOURSE study, a randomized, placebo-controlled, double-blind, multinational, phase 3 clinical trial that compared trifluridine plus tipiracil with best supportive care versus placebo plus best supportive care in 800 patients with relapsed metastatic colorectal cancer.[7,10]

Trifluridine plus tipiracil resulted in a significant 1.8-month improvement in median overall survival compared with placebo.[8,10] Furthermore, the oral combination was associated with few serious adverse events.[10]

Commenting on the approval, Richard Pazdur, MD,

Table 1 Targeted Drugs Approved for Colorectal Cancer

Drug class	Drug	Route of administration
VEGF inhibitors	Bevacizumab	Intravenous
	Ramucirumab	Intravenous
	Ziv-aflibercept	Intravenous
EGFR inhibitors	Cetuximab	Intravenous
	Panitumumab	Intravenous
Kinase inhibitors	Regorafenib	Oral

EGFR indicates epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Director of the FDA's Office of Hematology and Oncology Products, said, "The past decade has brought a new understanding around colorectal cancer, in how we can both detect and treat this often devastating disease. But there are many patients who still need additional options, and today's approval is a testament to the FDA's commitment to work with companies to develop new drugs in disease areas where unmet needs remain."[7]

Mechanism of Action

The newly approved cytotoxic agent is a combination of 2 new drugs—trifluridine, a thymidine-based nucleoside analog, and tipiracil, an inhibitor of thymidine phosphorylase. After uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis, and inhibits cell proliferation. Tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.[8]

Dosing and Administration

The trifluridine plus tipiracil tablet is provided in 2 dosage strengths—15 mg/6.14 mg and 20 mg/8.19 mg. The recommended dose of trifluridine and tipiracil is 35 mg/m^2, rounded up to the nearest 5-mg increment. It is dosed orally twice daily on days 1 through 5 and on days 8 through 12 of each 28-day cycle.[8]

Trifluridine plus tipiracil should be taken within 1 hour after the morning and the evening meals. Patients should not take additional doses of this oral agent to account for missed or held doses.[8] Patients should have blood cell counts done before and at day 15 of each cycle.

Because the trifluridine plus tipiracil combination tablet is a cytotoxic drug, patients should follow applicable special handling and disposal procedures.[8]

The RECOURSE Clinical Trial

The efficacy and safety of trifluridine plus tipiracil in metastatic colorectal cancer were demonstrated in the RECOURSE study, a multinational, randomized, double-blind, phase 3 clinical trial that compared trifluridine plus tipiracil with placebo in patients with metastatic disease that was refractory to antitumor therapy, or those who experienced clinically significant adverse events that precluded retreatment with those therapies.[7,10]

Among the 800 patients in the study, 534 patients received oral trifluridine plus tipiracil (35 mg/m^2) with best supportive care, and 266 patients received placebo plus best supportive care. Treatment was administered in 28-day treatment cycles—twice daily after the morning and evening meals for 5 days weekly, with a 2-day rest period for 2 weeks followed by a 14-day rest period.[8,10]

All patients received best supportive care, but did not receive other investigational antitumor agents or chemotherapy, hormonal therapy, or immunotherapy. Patients were evaluated every 2 weeks while receiving treatment, and every 8 weeks from the time they stopped treatment until death or until the clinical trial cutoff date for data collection.[10]

The primary end point was overall survival and the secondary end point was progression-free survival. Patients were stratified according to the tumor *KRAS* status (wild-type vs *KRAS* mutation), the time from first diagnosis of metastasis and study randomization (<18 months vs ≥18 months), and country of origin.[10]

The demographic and baseline characteristics were similar between the treatment arms. The majority of patients (median age, 63 years) were male (61%) and white (58%), with an ECOG performance status of 0 (56%).[10]

Overall, 51% of patients in RECOURSE had a *KRAS* mutation, and more than 60% had received ≥4 treatments for metastatic colorectal cancer. In addition, 93% of patients receiving trifluridine plus tipiracil had disease refractory to fluoropyrimidine-based therapy.[10]

The overall survival and progression-free survival were significantly improved in patients who received oral trifluridine plus tipiracil with best supportive care compared with patients receiving placebo plus best supportive care (**Table 2**).[8,10]

The median overall survival was 7.1 months among patients receiving trifluridine plus tipiracil versus 5.3 months with placebo, a significant difference (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.58-0.81; P <.001). The median progression-free survival was 2.0 months in the trifluridine plus tipiracil group and 1.7 months in the placebo group (HR, 0.47; 95% CI, 0.40-0.55; P <.001; Table 2).[8,10]

The clinical benefit observed with trifluridine plus tipiracil was consistent among the prespecified patient subsets, including patients with disease that had been refractory to fluorouracil when it was administered as a component of the treatment regimen before study entry, as well as in patients who had received regorafenib.[10]

Disease control (complete response, partial response,

stable disease), which was assessed at least 6 weeks after randomization, was achieved in 44% of trifluridine/tipiracil recipients and in 16% of placebo recipients (P <.001).[10]

Adverse Events

Patients in the RECOURSE study who received trifluridine plus tipiracil continued treatment for a mean 12.7 weeks. Approximately 14% of these patients required dose reductions, most often because of neutropenia, anemia, febrile neutropenia, fatigue, or diarrhea.[8]

Among all patients receiving trifluridine plus tipiracil, the most common nonhematologic adverse reactions (all grades) that occurred at a rate of >20%, and >2% higher than patients in the placebo arm included asthenia/fatigue (52% trifluridine plus tipiracil vs 35% placebo), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), and abdominal pain (21% vs 18%).[8]

The most common grade 3 or 4 nonhematologic toxicities associated with trifluridine plus tipiracil were asthenia or fatigue (7%) and decreased appetite (4%).[8]

Infections and pulmonary emboli also occurred more often with trifluridine plus tipiracil compared with placebo, including nasopharyngitis (4% vs 2%, respectively) and urinary tract infections (4% vs 2%, respectively).[8] Pulmonary emboli were reported in 2% of patients who received trifluridine plus tipiracil versus none with placebo.[8]

Hematologic toxicity (all grades) occurred more often with trifluridine plus tipiracil than with placebo, including anemia (77% vs 33%, respectively), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).[8]

Overall, 9% of patients who received trifluridine plus tipiracil required granulocyte colony-stimulating factor.[8,10]

Overall, 4% of patients receiving the study drug discontinued it because of adverse reactions compared with 2% in the control arm.[8,10] In addition, 1 patient in the trifluridine plus tipiracil arm died from septic shock.[10]

Trifluridine plus tipiracil has no contraindications, and formal drug interaction studies have not been conducted.[8]

Warnings and Precautions

Severe myelosuppression. Trifluridine plus tipiracil caused grade 3 or 4 myelosuppression, including neutropenia (38%), anemia (18%), thrombocytopenia (5%), and febrile neutropenia (4%).[8]

Complete blood counts should be obtained before starting therapy with trifluridine plus tipiracil, and on day 15 of each cycle or more frequently if indicated. The drug should be withheld if febrile neutropenia or grade 4 neutropenia occur, or if platelets decrease to <50,000/mm^3. Trifluridine plus tipiracil can be restarted at a reduced dose upon recovery.[8]

Table 2 The RECOURSE Trial: Trifluridine plus Tipiracil versus Placebo in Relapsed Metastatic Colorectal Cancer

Efficacy measure	Trifluridine + tipiracil and best supportive care (N = 534)	Placebo and best supportive care (N = 266)
Overall survival		
Deaths, N (%)	364 (68)	210 (79)
Median, mo	7.1 (95% CI, 6.5-7.8)	5.3 (95% CI, 4.6-6.0)
Hazard ratio	0.68 (95% CI, 0.58-0.81)	
	P <.001[a]	
Progression-free survival		
Events, N (%)	472 (88)	251 (94)
Median, mo	2.0 (95% CI, 1.9-2.1)	1.7 (95% CI, 1.7-1.8)
Hazard ratio	0.47 (95% CI, 0.40-0.55)	
	P <.001[a]	

[a]Stratified log-rank test (strata: *KRAS* status, time since diagnosis of first metastasis, region).

CI indicates confidence interval.

Sources: Lonsurf (trifluridine and tipiracil) tablets prescribing information; September 2015; Mayer RJ, et al. *N Engl J Med.* 2015;372:1909-1919.

Embryo-fetal toxicity. Based on animal studies and on its mechanism of action, trifluridine plus tipiracil can cause fetal harm when administered to a pregnant woman.[8]

Use in Specific Populations

Pregnancy. Based on animal data and on its mechanism of action, trifluridine plus tipiracil can cause fetal harm.[8]

Lactation. It is not known whether trifluridine plus tipiracil or its metabolites are present in human milk.[8] Women should not breast-feed during treatment with this agent and for 1 day after completing therapy.[8]

Reproductive potential. Females of reproductive potential should use effective contraception during treatment with trifluridine plus tipiracil. Males with female partners of reproductive potential should use condoms during treatment with this agent and for at least 3 months after the final dose.[8]

Pediatric use. Trifluridine plus tipiracil was not studied in pediatric patients.[8]

Geriatric use. Of the 533 patients who received trifluridine plus tipiracil in the RECOURSE study, 44% were aged ≥65 years, and 7% were aged ≥75 years. No overall efficacy differences were observed between younger and older patients; no adjustment to the starting dose is recommended based on age.[8]

Patients aged ≥65 years who received trifluridine plus

tipiracil had a higher incidence of specific adverse events compared with younger patients, including grade 3 or 4 neutropenia, grade 3 anemia, and grade 3 or 4 thrombocytopenia.[8]

The RECOURSE study demonstrated that the addition of trifluridine plus tipiracil to best supportive care significantly enhanced overall survival and progression-free survival compared with best supportive care alone in the salvage metastatic colorectal cancer setting.

Hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of trifluridine plus tipiracil is not known. No dose adjustment is recommended for patients with mild hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the RECOURSE study.[8]

Renal impairment. The effect of renal impairment on the pharmacokinetics of trifluridine plus tipiracil is not known. No adjustment to the starting dose is recommended in patients with mild or moderate renal impairment. Patients with severe renal impairment were excluded from the RECOURSE study.[8]

Ethnicity. There were no clinically meaningful differences in adverse event rates in the RECOURSE study between Western and Asian patients.[8]

Conclusion

Trifluridine plus tipiracil is the second oral therapy to be approved for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild-type, an anti-EGFR therapy. The FDA approval of a second oral treatment option for this patient population adds a convenient treatment option for patients with advanced colorectal cancer.

The RECOURSE study demonstrated that the addition of trifluridine plus tipiracil to best supportive care significantly enhanced overall survival and progression-free survival compared with best supportive care alone in the salvage metastatic colorectal cancer setting. Additional clinical studies are exploring the activity of trifluridine plus tipiracil in advanced colorectal cancer, as well as in other solid tumors.[11] ■

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